

**REMARKS**

The Office Action mailed March 27, 2003, has been received and its contents carefully noted. The pending claims, claims 1-19, were rejected. By this amendment, claims 1-19 have been amended. Support may be found in the specification and claims as originally filed. No statutory new matter has been added. Reconsideration is respectfully requested.

**Rejection under 35 U.S.C. §112, second paragraph**

The Examiner rejected claims 1-19 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner deemed that:

1. Claims 1-3 are vague because it is not clear whether the test consists of an assay method.
2. Claim 3 is vague because it is unclear as to what "other corresponding antibody methods" refer to.
3. Claim 4 is unclear as to how the body fluid or tissue sample is being prepared.
4. Claim 7 lacks antecedent basis for "the mixture" and "the product".

5. Claim 7 is unclear because step "d" does not explain how the content of cis-4-hydroxyproline and its derivative content are determined.

6. Claim 13 lacks antecedent basis for "the quantitative analysis".

Applicant respectfully submits that the claims as amended obviate the rejection. Therefore, the rejection under 35 U.S.C. 112, second paragraph, should properly be withdrawn.

**Rejection under 35 U.S.C. § 102(b)**

The Examiner rejected claims 1-6 and 14 under 35 U.S.C. 102(b) as being anticipated by Sessa et al. (1986) Journal of Chromatography 382:258-263 (Sessa et al.). Specifically, the Examiner deemed that Sessa et al. teaches methods to quantify various isomers (derivatives) of hydroxyprolines in body fluid such as urine and plasma through ion-exchange and chromatography.

Applicant respectfully submits that the Examiner fails to appreciate the significance of the present invention and the limited teachings of Sessa et al. Specifically, the present inventor was the first one to recognize that cis-hydroxyproline, particularly cis-4-hydroxyproline, must be considered an endogenic substance. At the time Sessa et al. was published (and even after that), those skilled in the art strongly

believed that only trans-hydroxyproline, especially trans-4-hydroxyproline, is a substance, and for this reason, only trans-hydroxyproline has been subject for the purpose of analysis and studies. This is supported by the fact that, contrary to trans-hydroxyproline, no single document about endogenic cis-hydroxyproline has ever been published. Since cis-hydroxyproline had not been known, Sessa et al. simply could not have intended to measure the content of cis-hydroxyproline in the body.]

*Can't argue invention of PEP.*

Instead, the aim of Sessa et al. was to determine the content of trans-4-hydroxyproline in tissue samples as the marker substance for the quantification of collagen. See page 258, first paragraph. As can be seen from page 259, last paragraph, neutralized hydrolysate was placed into a test tube, then cis-4-hydroxyproline was added to each sample as an internal standard. Such addition of exogenic cis-4-hydroxyproline is a convenient method to quantify trans-4-hydroxyproline. As given on page 260, same paragraph, total hydroxyproline was determined by comparing the ratio of peak heights of trans-4-hydroxyproline/cis-4-hydroxyproline to those ratios, which have been generated by standards.

In other words, in contrast to the present invention, Sessa et al. did not quantify the concentration of cis-4-hydroxyproline. Indeed, Sessa et al. even did not quantify any

*cis*-4-hydroxyproline (exogenic), but only the ratio of its trans-isomer to its cis-isomer to determine the content of total hydroxyproline. The value from the content of *trans*-4-hydroxyproline could easily be obtained by simply subtracting the known content of externally added *cis*-4-hydroxyproline.

Furthermore, since Sessa et al. did already know the content of *cis*-4-hydroxyproline (a known amount had been added externally), there was also no need at all to detect and measure *cis*-4-hydroxyproline.

Nowhere do Sessa et al. teach or suggest the present claims as amended, i.e. methods and kits for detecting or measuring *cis*-4-hydroxyproline. Therefore, the rejection under 35 U.S.C. 102(b) should properly be withdrawn.

#### **Rejection under 35 U.S.C. § 103(a)**

The Examiner rejected claims 7-13 and 15 under 35 U.S.C. 103(a) as being unpatentable over Sessa et al. Specifically, the Examiner deemed that although Sessa et al. does not teach performing the instant process in sequential order, it would have been obvious to one of ordinary skill in the art to use equivalent reagents because they yield equivalent results as that of the instant claimed process, and detection of known hydroxyprolines utilizing known reagents is a routine optimization of the method of Sessa et al., and using an

internal standard or control in a modified form only requires routine skill in the art.

Applicant respectfully submits that as explained above, nowhere do Sessa *et al.* teach or suggest detecting or measuring cis-4-hydroxyproline. Since cis-4-hydroxyproline was not known to be an endogenic substance prior to the present invention, one of ordinary skill in the art would not be motivated to detect or measure cis-4-hydroxyproline in a body fluid or a tissue sample with a reasonable expectation of success. Especially important is also the determination of cis-hydroxyproline, according to the invention, for the purpose of following the course of development of the disease, a feature that is also important to the evaluation of the efficacy of the therapeutic measures and their dosing. Therefore, the rejection under 35 U.S.C. 103(a) should properly be withdrawn.

**Request for Interview**

Applicant respectfully requests either a telephonic or an in-person interview should there be any remaining issues.

**Extension of Time**

A Petition for an Extension of Time for one (1) month under 37 C.F.R. 1.136 and the appropriate fee are submitted herewith to extend the time for responding to the Office Action to July 27, 2003.

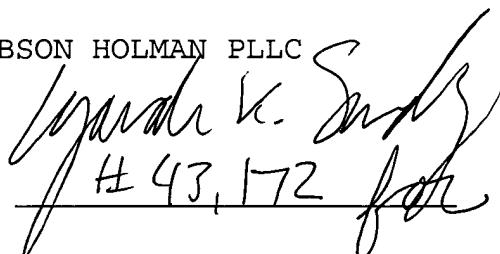
**Conclusion**

In view of the foregoing amendments and remarks, the Examiner is respectfully requested to reconsider and withdraw the rejection of the claims and to find this application to be in allowable condition.

Respectfully submitted,

JACOBSON HOLMAN PLLC

By



A handwritten signature in black ink, appearing to read "Harvey B. Jacobson, Jr." with "H-43,172" written below it.

Harvey B. Jacobson, Jr.  
Reg. No. 20,851

400 Seventh Street, N.W.  
Washington, D.C. 20004-2201  
(202) 638-6666  
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